Biology of Blood and Marrow Transplantation 11:223–230 (2005)

1083-8791/05/1103-0008$30.00/0
doi:10.1016/j.bbmt.2004.12.328

Prediction and Prevention of Transplant-Related Mortality from Pulmonary Causes after Total Body Irradiation and Allogeneic Stem Cell Transplantation

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Received November 2, 2004; accepted December 17, 2004

ABSTRACT

Between July 1997 and August 2004, 146 consecutive patients with hematologic malignancies received a T cell–depleted peripheral blood stem cell transplant from an HLA-identical sibling by using total body irradiation (TBI) and cyclophosphamide conditioning regimens. Eighty-five patients received 13.6 Gy of TBI with no lung shielding, and 61 received lung shielding (total lung dose, 6-12 Gy). Ninety-four patients (65.5%) had standard-risk disease; the remainder had more advanced disease or unfavorable diagnoses. Of the 21 transplant-related deaths, 14 were from pulmonary causes (10 idiopathic pulmonary syndromes and 4 from infection) that occurred at a median of 90 days (range, 23-238 days) after transplantation. Independent risk factors for pulmonary transplant-related mortality (PTRM) were pretransplantation diffusion capacity for carbon monoxide (relative risk, 5.7 for diffusion capacity for carbon monoxide <85%), smoking (relative risk, 5.0), and CD34 cell dose (relative risk, 9.4 for a CD34 dose of $<5 \times 10^6$ cells per kilogram). Patients receiving lung shielding had significantly lower PTRM (3.3% versus 14.1%; $P = .02$) and better overall survival (70% ± 6% versus 52% ± 5%; $P = .04$), but lung shielding was not a significant independent factor for determining PTRM. These results suggest that pulmonary mortality after TBI-based preparative regimens is predictable and that higher CD34 cell doses can reduce the risk.

KEY WORDS

Pulmonary complications • Stem cell transplantation

INTRODUCTION

Although allogeneic stem cell transplantation (SCT) is the only curative treatment for some hematologic malignancies, success is limited by transplant-related mortality (TRM). Although reduced-intensity transplant conditioning regimens result in improved regimen-related toxicity, they are less effective at disease control [1]. Intensive conditioning regimens using total body irradiation (TBI) remain the most effective way to prevent relapse of disease after transplantation. However, approximately 20% of patients given such myeloablative conditioning regimens die of transplant-related causes [1,2]. Although multiple factors such as infection, graft-versus-host disease (GVHD) and its treatment, and regimen-related toxicity contribute to TRM, the most frequent proximal causes of death are ventilatory failure, hepatic failure, and major injury to the central nervous system. Because the prevention and treatment of GVHD and infection have improved, regimen-related toxicity accounts for an increasing proportion of TRM after SCT.

Because death related to pulmonary failure has been the major contributor to TRM in transplant recipients given TBI conditioning regimens, we investigated ways to predict pulmonary TRM (PTRM) by studying pretransplantation patient characteristics and measuring pulmonary function. In an attempt to reduce PTRM, we also introduced lung shielding to limit the TBI dose to the lungs. Here we describe factors that determine PTRM and describe a favorable transplantation outcome in recipients of TBI with lung shielding.

MATERIALS AND METHODS

Study Group

Between July 1997 and August 2004, 146 consecutive patients with hematologic malignancies received a T cell–depleted peripheral blood SCT (PBSCT) from an HLA-identical sibling in 5 successive National Heart, Lung, and Blood Institute (NHLBI) institutional review board–approved protocols (97-H-0099, 99-H-0046, 02-H-0111, 03-H-0192, and 04-H-0112). Patients were studied to identify the effect of pretransplantation and transplantation characteristics on PTRM.

Conditioning Regimens

Three conditioning regimens were used in consecutive time periods: regimen A consisted of 13.6 Gy of TBI and cyclophosphamide 120 mg/kg, with no lung shielding, from April 1997 to December 2001 (n = 85). Regimen B consisted of 12.0 Gy of TBI with lung shielding (9.0 Gy to lungs), cyclophosphamide 120 mg/kg, and fludarabine 125 mg/m^2 from February 2002 to May 2003 (n = 35). Regimen C consisted of 12.0 Gy of TBI with lung shielding (6.0 Gy to lungs), cyclophosphamide 120 mg/kg, and fludarabine 125 mg/m^2 from June 2003 to August 2004 (n = 26). Patients who received lung shielding had dosage boosts given to the mediastinum.

Transplantation Approach

In the first protocol (97-H-0099), patients received a T cell–depleted granulocyte colony-stimulating factor–mobilized PBSCT by using the Ceprate selection system (CellPro, Bothell, WA). Subsequent protocols used an Isolex 300 cell separator as previously described [3]. CD34 cells were positively selected by using anti-CD34 beads, and residual T cells were removed with a cocktail of anti-CD2, -CD6, and -CD7 antibody-coated beads. The CD34 cell dose ranged from 2.45 to 15.90 $\times$ 10^6/kg (median, 5.0 $\times$ 10^6/kg); the T-cell dose was 0.2 to 1.0 $\times$ 10^5 CD3 cells per kilogram recipient weight. In the absence of GVHD or unless molecular remission was documented in chronic myeloid leukemia (CML), T cells were added back on day 45 and 100 (n = 140) or day 60 (n = 6). The cyclosporine (CSA) dose varied according to protocol: 36 received standard-dose CSA (target plasma level, 200-400 ng/mL); 20 received low-dose CSA (target plasma level, 100-200 ng/mL), starting on day −4 and continuing until an oral dose was tolerated; and 90 received no CSA during the first 6 weeks after transplantation. All patients started CSA either on day +44 (if T cells were added back on day +45) or on day +59 (if T cells were added back on day 60), and it was continued until at least day +130 (or longer, if chronic GVHD occurred). Standard prophylaxis against infection included fluconazole to day 100, co-trimoxazole for 6 months after transplantation, and weekly surveillance for cytomegalovirus antigenemia, as described previously [3,4]. Acute GVHD was managed with high-dose steroids. Steroid-refractory patients (no response to 7 days of treatment) received combined treatment with anti–tumor necrosis factor (infliximab) and anti-CD25 (daclizumab) monoclonal antibodies, as described previously [5].

Diagnosis and Management of Posttransplantation Pulmonary Complications

Bronchioalveolar lavage (BAL) was performed on all patients with undiagnosed pulmonary infiltrates. Specimens obtained were submitted for microbiologic cultures and cytopathologic examination. Pulmonary mortality from infectious causes was defined as death from bacterial, viral, or fungal pneumonia or pneumonitis after positive culture or by confirmation at autopsy. Acute respiratory distress syndrome (ARDS) was defined as acute-onset shortness of breath with hypoxia and increased vascular permeability manifested by bilateral pulmonary infiltrates, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of ≤200 mm Hg regardless of positive end-expiratory pressure, and no evidence of an increased left atrial pressure. Pulmonary hemorrhage was diagnosed during bronchoscopy and defined as diffuse alveolar pulmonary infiltrates with increasing bloody return on sequential aliquots of BAL. Interstitial pneumonitis (IP) was defined as bilateral pulmonary infiltrates with profound hypoxia after exclusion of other causes by BAL or by autopsy. IP and ARDS were grouped as idiopathic pneumonia syndrome (IPS) as defined by an NHLBI workshop [6]. Patients who developed pulmonary failure were transferred to intensive care and supported on a ventilator.

Pulmonary Function Tests

Baseline pulmonary function tests (PFTs) were obtained in all patients 5 to 21 days before PBSCT. Ventilatory capacity was measured by forced vital capacity, forced expiratory volume in the first second (FEV1), the FEV1/forced vital capacity ratio, and peak expiratory flow. Lung volume measurements (by helium dilution) included vital capacity (VC), total lung capacity, residual volume, and the residual volume/total lung capacity ratio. Diffusion capacity for carbon monoxide (DLCO) was determined by using a carbon monoxide single-breath technique with correction for hemoglobin concentration. PFTs were expressed as a percentage of the predicted values in healthy controls with corresponding age, sex, and smoking habits. Eligibility criteria for enrollment into protocols included DLCO ≥60% of predicted.

Risk Factors for Pulmonary Complications

Patients with CML in first chronic phase, acute leukemia in first remission, and myelodysplastic syndrome with refractory anemia or refractory anemia with excess blasts were categorized as standard risk for transplant-related complications. All other patients were considered at high risk for transplant-related complications. Smokers were defined as patients who regularly smoked within 2 months before PBSCT for a minimum of 2 years. Busulfan treatment in patients with CML was defined as more than 30 days of busulfan treatment before transplantation.

Statistical Methods

Summary statistics, such as proportions, means, standard deviations, 95% confidence intervals, medians, and ranges, were used to describe the patient characteristics, pretransplantation variables, and post-transplantation outcomes. Kaplan-Meier estimates and Cox proportional hazard models were used to estimate the time-to-event distributions of overall survival, relapse-free survival, TRM, and PTRM. In particular, Kaplan-Meier curves were used to display the distributions of survival and mortality among subgroups of patients, and Cox proportional hazard models with univariate or multivariate covariates were used to evaluate the effects of covariates, such as smoking, DLCO, and disease risk, on survival times. Statistical associations between pretransplantation variables were investigated by using correlation analysis, including Pearson correlation coefficients and Spearman rank correlation coefficients, and multiple regression analysis. Statistical tests based on t tests, χ^2 tests, and F tests were used to evaluate the statistical significance of covariates in multiple regression models or Cox proportional hazard models. The Wald score and likelihood ratio tests were used to evaluate the fitness of the Cox proportional hazard models. Data analysis was performed with Splus (Insightful Corp, Seattle, WA) and SPSS 12 for Windows (SPSS Inc., Chicago, IL) software.

RESULTS

Patient characteristics are summarized in Table 1. The median follow-up was 1331 days (range, 92-2723 days), and more than half of the surviving patients were followed up for at least 3 years after transplantation. The actuarial overall survival, relapse-free survival, TRM, and PTRM of the study group were 58% ± 4%, 53% ± 4.5%, 16% ± 3%, and 10.5% ± 2.5%, respectively (Figure 1). PTRM occurred in 14 patients, accounting for 67% of all TRM. The characteristics of patients with PTRM are detailed in Table 2. The cause of PTRM was investigated by BAL or lung biopsy or at autopsy in all patients. Ten patients died from IPS (IP, n = 6; ARDS, n = 4), and 4 patients died from non-IPS infectious pulmonary causes. The overall TRM from IPS and non-IPS causes was 6.8% and 2.7%, respectively (Table 3). The median time to PTRM was 90 days (IPS, 70 days; non-IPS, 174 days). Ten patients died of IPS between 23 and 218 days after PBSCT (median, 70 days). Eight of these died before day 100 after transplantation.

Pretransplantation Factors Affecting PTRM

Univariate analysis showed that the pretransplantation variables smoking, prior busulfan (in CML patients), DLCO/FEV1/VC (<85% of predicted), and high-risk disease were associated with increased PTRM (Table 1). Age, sex, race, and diagnosis did not significantly affect the risk of PTRM. The DLCO, FEV1, and VC were highly correlated (correlation coefficients of 0.443, 0.280, and 0.217, respectively, and P values of <.0001, .001, and .008, respectively), but the parameter most predictive of outcome was DLCO. Of 47 patients with DLCO <85% of predicted and 99 patients with DLCO ≥85% of predicted, 11 versus 3 had PTRM ($P < .0001$), and 10 versus 0 had IPS ($P < .0001$), respectively. The high-risk group had a higher overall PTRM (9 of 52 versus 5 of 94; $P = .02$) and IPS-related PTRM (7 of 52 versus 3 of 94; $P = .02$). Actuarial survival of the high-risk group was 24.5% ± 6% compared with 75% ± 5% in the standard-risk group ($P <$ .0001). Smokers had a higher PTRM (8 of 21 versus 6 of 125; $P = < .0001$), IPS (5 of 21 versus 5 of 125; $P =$ .006), and non-IPS PTRM (3 of 21 versus 1 of 125; $P =$ .009). Seven of 56 CML patients had received prior busulfan. Four of 7 in the busulfan group compared with 2 of 49 in the no-busulfan group had PTRM ($P = .001$). Similarly, there was significantly higher mortality from IPS in the busulfan group: 3 of 7 versus 1 of 49 ($P <$ .0001). In multivariate analysis, 2 pretransplantation factors identified as significant in univariate analysis were found to be independent variables predictive for PTRM: DLCO <85% and a positive smoking history, with a relative risk of 5.7 and 5.0, respectively (Table 4). The DLCO and smoking were not correlated (correlation coefficient, −0.079; $P = .344$).

Transplant-Related Factors Affecting PTRM

A higher CD34 dose (more than the median of 5.0×10^6 $CD34^+$ cells per kilogram) was associated with a significant reduction in PTRM (1 of 73 versus 13 of 73; $P = .001$) and IPS (1 of 73 versus 9 of 73; $P = .009$). CSA and T-cell dose did not affect the risk of PTRM (Table 1). CD34 dose was also found to be an independent risk factor for PTRM in multivariate analysis (patients receiving $<5 \times 10^6$ CD34 cells per kilogram had a relative risk of 9.4 for PTRM; Table 4).

In univariate analysis, a higher lung radiation dose (no lung shielding) and a lower CD34 dose were associated with a statistically significantly increased

Table 1. *Patient Characteristics and Results of Univariate Analysis*

Variable	No. Patients (%)	Pulmonary TRM, n (%)	*P* Value	IPS, n (%)	*P* Value	Non-IPS, n (%)	*P* Value
Pretransplantation variables							
Age, y (range, 10-56; median, 34)			.26		.63		.06
<34	73	5 (7)		5 (7)		0 (0)	
≥34	73	9 (12)		5 (7)		4 (6)	
Sex			.93		.41		.44
Female	61 (42)	6 (10)		5 (8)		1 (2)	
Male	85 (58)	8 (9)		5 (6)		3 (4)	
Race			.60		.15		.63
Asian	24 (16)	4 (17)		4 (17)		0 (0)	
African American	14 (10)	1 (7)		0 (0)		1 (7)	
Hispanic	67 (46)	5 (8)		3 (5)		2 (3)	
White	41 (28)	4 (10)		3 (7)		1 (2)	
Disease group			.16		.47		.001
CML	56 (38)	6 (11)		5 (9)		1 (2)	
AML	38 (26)	5 (13)		4 (11)		1 (3)	
MDS	23 (16)	1 (4)		1 (4)		0 (0)	
ALL	22 (15)	0 (0)		0 (0)		0 (0)	
Other	7 (5)	2 (29)		0 (0)		2 (29)	
Conditioning regimens			.07		.24		.23
A	85 (58)	12 (14)		8 (10)		4 (5)	
B	35 (24)	2 (6)		2 (6)		0 (0)	
C	26 (18)	0 (0)		0 (0)		0 (0)	
Disease risk			.02		.02		.45
High	52 (36)	9 (17)		7 (14)		2 (4)	
Standard	94 (64)	5 (5)		3 (3)		2 (2)	
Smoking			<.0001		.006		.009
Yes	21 (14)	8 (38)		5 (24)		3 (14)	
No	125 (86)	6 (5)		5 (4)		1 (1)	
Prior busulfan*			.001		<.0001		.88
Yes	7 (13)	4 (57)		3 (43)		1 (14)	
No	49 (87)	2 (4)		1 (2)		1 (2)	
DLCO (% predicted) (terciles)			<.0001		<.0001		.79
<85	47 (32)	11 (23)		10 (21)		1 (2)	
85-94	50 (34)	2 (4)		0 (0)		2 (4)	
>94	49 (34)	1 (2)		0 (0)		1 (2)	
Transplantation variables							
Lung shielding (lung dose)			.02		.13		.11
Yes (<1360 cGy)	61 (42)	2 (3)		2 (3)		0 (0)	
No (>1360 cGy)	85 (58)	12 (14)		8 (9)		4 (5)	
CD34 dose (million cells/kg) (median)			.001		.009		.06
<5.0	73	13 (18)		9 (12)		4 (6)	
≥5.0	73	1 (1)		1 (1)		0 (0)	
CSA dose			.74		.85		.42
N	90 (61)	9 (10)		7 (8)		2 (2)	
LD	20 (14)	1 (5)		1 (5)		0 (0)	
SD	36 (25)	4 (11)		2 (6)		2 (6)	
T-cell dose			.07		.17		.21
2×10^4	61 (41)	2 (3)		2 (3)		0 (0)	
5×10^4	49 (34)	8 (16)		6 (12)		2 (4)	
1×10^5	36 (25)	4 (11)		2 (6)		2 (6)	

CML indicates chronic myeloid leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; N, no cyclosporine; LD, low dose; SD, standard dose.

*CML patients only.

risk of PTRM (Table 1). When comparing lung-shielded (regimens B and C) versus nonshielded (regimen A) regimens, a higher PTRM was seen in non–lung-shielded transplantations (12 of 85 versus 2 of 61; $P = .02$). There was no difference in PTRM between regimens B and C (lung dose: 900 versus 600 cGy) or between regimens A and B versus C (lung dose: >600 versus 600 cGy), although only 2 of 35 patients in regimen B (lung dose: 900 cGy) and 0 of 26 in regimen C (lung dose: 600 cGy) had PTRM. There was a

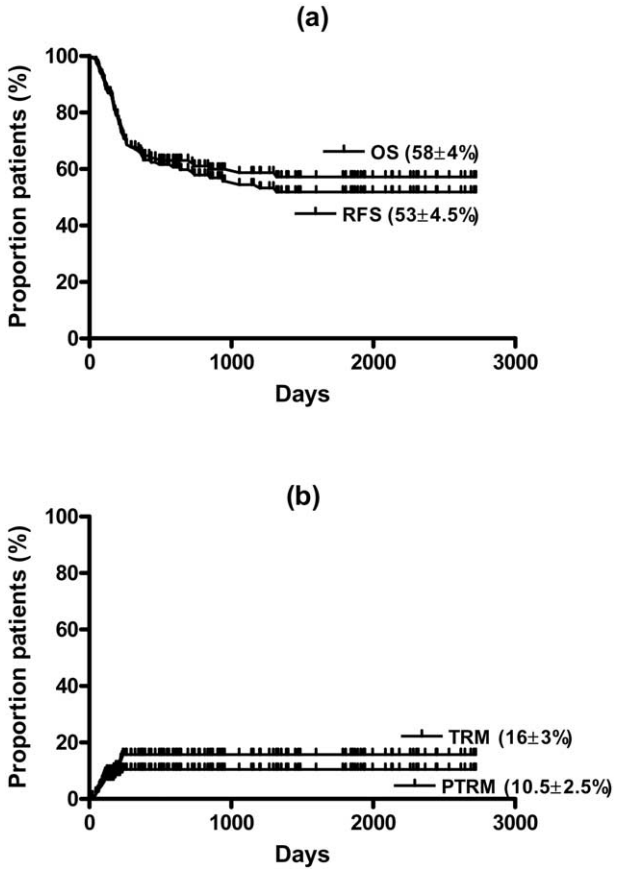

Figure 1. Overall survival (OS) and relapse-free survival (RFS) (A) and transplant-related mortality (TRM) and pulmonary TRM (PTRM) (B) for the 146 patients studied.

significant survival advantage with lung shielding (70% ± 6% versus 52% ± 5%; $P = .04$) that was due to less PTRM in this group and a trend to improved relapse-free survival (60% ± 7% versus 36% ± 8%; $P = .07$) in lung-shielded patients. However, lung shielding did not emerge as an independent predictive factor for PTRM in multivariate analysis.

Table 3. *Causes of PTRM*

PTRM	n	%
IPS	10	6.8
IP	6	4.1
ARDS	4	2.7
Non-IPS	4	2.7
CMV	2	1.4
RSV	1	0.7
Bacterial	1	0.7
Total PTRM	14/146	9.6

PTRM indicates pulmonary transplant-related mortality; IPS, ideopathic pneumonia syndrome; IP, interstitial pneumonitis; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; RSV, respiratory syncytial virus.

DISCUSSION

Historically, pulmonary complications have been a major cause of morbidity after allogeneic SCT. They occur in 40% to 50% of patients and have a mortality of 30% to 50% [7-13]. The spectrum of pulmonary complications includes infectious and noninfectious etiologies. Common early complications include pulmonary edema, infectious pneumonia, IP, ARDS, and diffuse alveolar hemorrhage. Noninfectious pulmonary complications are a particular concern because they respond poorly to standard therapeutic approaches and contribute substantially to TRM. An NHLBI workshop defined widespread alveolar injury after SCT that occurs in the absence of an active lower respiratory tract infection and

Table 2. *Characteristics of Patients with PTRM*

Patient No.	Age (y)	Sex	Diagnosis	Disease Risk	Smoking	Busulfan*	DLCO (%)	Lung Dose (cGy)	CD34 Dose ($\times 10^4$/kg)	CSA Dose	T-Cell Dose/kg	Survival (d)	Pulmonary TRM
5	47	F	MDS	SR	N	—	68	1360	4.63	SD	1×10^5	71	IP
7	48	M	CML	SR	Y	N	92	1360	4.84	SD	1×10^5	238	CMV
9	47	M	MM	HR	Y	—	87	1360	3.72	SD	1×10^5	172	RSV
11	30	F	CML	HR	N	Y	69	1360	4.42	SD	1×10^5	90	IP
37	35	F	AML	HR	N	—	70	1360	4.27	N	5×10^4	46	IP
39	37	F	AML	HR	N	—	110	1360	3.70	N	5×10^4	187	CMV
42	37	M	AML	HR	Y	—	72	1360	4.74	N	5×10^4	23	ARDS
47	21	M	CML	HR	Y	Y	68	1360	3.68	N	5×10^4	108	IP
51	44	M	CLL	SR	Y	—	74	1360	3.80	N	5×10^4	103	Bacterial
52	13	F	CML	HR	N	Y	64	1360	4.51	LD	5×10^4	69	IP
55	34	M	CML	SR	Y	N	74	1360	12.80	N	5×10^4	44	ARDS
57	44	M	AML	SR	Y	—	68	1360	3.09	N	5×10^4	216	ARDS
88	21	M	CML	HR	Y	Y	72	900	4.86	N	2×10^4	89	ARDS
89	41	F	AML	HR	N	—	68	900	2.72	N	2×10^4	60	IP

M indicates male; F, female; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; MM, multiple myeloma; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; SR, standard risk; HR, high risk; Y, yes; N, no; DLCO, diffusion capacity for carbon monoxide; CSA, cyclosporine; SD, standard dose; N, no cyclosporine; LD, low dose; IP, interstitial pneumonitis; CMV, cytomegalovirus; RSV, respiratory syncytial virus; ARDS, acute respiratory distress syndrome.

*CML patients only.

Table 4. *Multivariate Cox Regression Analysis of Risk Factors for PTRM*

Factor	Estimate of Coefficient (β)	Relative Risk (e^{β})	95% Confidence Interval for Relative Risk	*P* Value for β = 0
DLCO (% predicted)				
≥85		1.00		
<85	1.74	5.7	1.95-16.75	.001
Smoking				
No		1.00		
Yes	1.61	5.0	1.57-15.97	.001
CD34 dose				
≥5.0 million cells/kg		1.00		
<5.0 million cells/kg	2.24	9.4	1.15-76.26	.03

cardiogenic causes as IPS [6]. In this study, we have therefore included IP and ARDS in the category of IPS as defined by the NHLBI workshop. The actuarial probability of PTRM in our study was 10.4% ± 2.7%, with 6.4% death due to IPS, and this is within the range reported in the literature [14-16]. In a meta-analysis of 12 studies of 4496 patients summarized by Afessa et al., [17] the overall incidence of IPS was 10% (range, 2%-17%). It varied with the patient population studied, with differences in the diagnostic methods used, and by the lack of a uniform definition of IPS. The mortality rate estimate was 74% (range, 60%-90%) regardless of therapy. In this analysis, the proportion of patients who died of IPS was high (67% of all PTRM) compared with previous reports [18]. The higher proportion of noninfectious causes of PTRM may reflect improved outcome for infectious pulmonary complications: in our study, only 2.7% patients died from infectious pulmonary complications.

Earlier studies have sought to define risk factors for severe pulmonary complications that lead to PTRM, included conditioning with TBI (lung shielding versus no shielding), GVHD, older recipient age, use of methotrexate for GVHD prophylaxis, pre-SCT impaired pulmonary function as measured by PFTs, more advanced disease status, HLA disparity, longer duration from diagnosis to SCT, and decreased pre-SCT performance status [7,10,11,13,19-26]. Some of these factors were shown to be independent variables in multivariate analysis.

Several studies have described an association of IPS and GVHD [10,11,13,17-19,24,27] and have suggested that GVHD may synergize with regimen-induced lung damage to cause IPS. Murine models show that alloreactive T cells and radiation conditioning induce GVHD and IPS under conditions in which neither could do so individually [28,29]. Clinical evidence also suggests that both non–immune-mediated and immune-mediated lung injury contribute to the development of IPS, because despite a comparable incidence of GVHD, IPS frequency was lower after nonmyeloablative conditioning than after a conventional myeloablative regimen [22]. In our study, none of the 14 patients who died of PTRM had significant GVHD.

There is a general perception that over the last decade, TRM and associated PTRM have diminished in part because of more effective management of infectious complications (especially cytomegalovirus [30]), reduced-intensity conditioning regimens, [13,17,22] and lung shielding during TBI [31-34]. This analysis evaluated risk factors for PTRM in the context of these improvements. We found that pretransplantation smoking history, busulfan exposure in CML patients, and, most notably, PFTs can predict which patients are at risk from PTRM. Of these factors, smoking and decreased DLCO (<85% of predicted) were found to be independent risk factors that increased the risk of PTRM 5.0- and 5.7-fold, respectively. Our study showed a strong correlation between DLCO, FEV1, and VC and PTRM. We selected DLCO as the most useful predictive parameter because reduced diffusion capacity most closely reflects the main pathology (reduced oxygenation from reduced diffusion) in mechanically ventilated patients dying from pulmonary failure. Our results concord with previous reports that demonstrated an association between pretransplantation PFT and early mortality after SCT [15,24,35,36]. Crawford and Fisher [35] studied the predictive value of pretransplantation PFTs and pulmonary morbidity after SCT. They found that DLCO <80% of predicted was significantly associated with mechanical ventilation and death after transplantation. However, Ghalie et al. [16] found no association between abnormal pretransplantation PFT and fatal pulmonary complications. It cannot be excluded from our data that pretransplantation PFTs were a surrogate for other mechanisms of tissue damage that affect mortality (eg, diminished diffusion capacity as a marker of diffuse endothelial injury or potential for hepatic veno-occlusive disease [37]).

It is interesting to note that pretransplantation smoking was associated with significantly increased PTRM in our analysis (38% versus 4.8%; $P < .0001$). This contrasts with a study by Ho et al., [36] who found that tobacco use was not associated with increased severe pulmonary complications after allogeneic SCT. Busulfan was associated with a significantly increased risk of PTRM (4 of 7 versus 2 of 49; $P < .0001$). Low DLCO, smoking, and busulfan were not

correlated, thus indicating that busulfan was an independent risk factor for PTRM in CML.

High-risk disease was associated with increased PTRM in univariate analysis only in our study. Other investigators found no association between disease risk and IPS [22] or early pulmonary complications [36].

An assessment of DLCO and smoking history may identify patients at risk from PTRM who might benefit most from reduced lung irradiation, higher CD34 transplant doses, and efficient GVHD prophylaxis to reduce the risk of pulmonary damage after SCT. The effect of these factors on PTRM requires further validation in prospective studies.

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